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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,054	CRABTREE ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-24 and 40-64* is/are pending in the application.

4a) Of the above claim(s) *40-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *16-24 and 40-64* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicants response to the Office Action mailed 4 October 2004 is acknowledged. In the amendment filed therein claims 1-15 and 25-39 were cancelled. New claims 40-64 have been added. The new claims necessitated the following restriction requirement:

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 16-24, are drawn to a method of inhibiting the binding of a target protein (T) and a binding protein (P) *in vivo* via the administration of bifunctional inhibitor molecule of less than 5000 daltons consisting of a target protein ligand and blocking protein ligand (B), where in the target protein ligand specifically binds (T) and the blocking protein ligand specifically binds (B), classified in class 436, subclass 518 for example.

II. Claims 40-48, are drawn to a method of inhibiting the binding of a target protein (T) and a binding protein (P) *in vivo* via the administration of bifunctional inhibitor molecule of less than 5000 daltons consisting of a target protein ligand and blocking protein ligand (B), where in the target protein ligand specifically binds (T) with a binding affinity of at least about 10^{-4} M and the blocking protein ligand specifically binds (B) with a binding affinity of at least about 10^{-4} M, classified in class 436, subclass 518 for example.

III. Claims 49-55, are drawn to a method of inhibiting the binding of a target protein (T) and a binding protein (P) *in vivo* via the administration of bifunctional inhibitor molecule of less than 5000 daltons consisting of a target protein ligand and blocking protein ligand (B), where in the target protein ligand specifically binds (T) at least about 10^{-4} M and the blocking protein ligand is a peptidyl-prolyl isomerase that specifically binds (B), classified in class 436, subclass 518 for example.

IV. Claims 56-64, are drawn to a method of inhibiting the binding of a target protein (T) and a binding protein (P) *in vivo* via the administration of bifunctional inhibitor molecule of less than 5000 daltons consisting of a target protein ligand and blocking protein ligand (B), where in the target protein ligand *is known to* specifically binds (T) and the blocking protein ligand *is known to* specifically binds (B), classified in class 436, subclass 518 for example.

3. The inventions are distinct, each from the other because of the following reasons:

The method inventions of I, II, III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different methods inventions (I, II, III, IV) are not disclosed as capable of use together and have different modes of operation.

The method of group I utilizes a target protein ligand and blocking protein ligand which specifically bind (T) and (B) respectively (*reading on known and unknown binding specificity*). However the method of group II uses ligands with a specified binding affinity of at least about 10^{-4}M. The invention of group III requires the target protein ligand to specifically bind with an affinity of at least about 10^{-4}M while the blocking protein ligand is a peptidyl-prolyl isomerase. The invention of group IV is further distinct because it employs ligands that are *known to* specifically bind their targets (T) or (B). Accordingly, the methods require different reagents having patentably diverse and distinct binding requirements. Each limitation requires a different search and separate considerations. Therefore the methods are independent and distinct inventions utilizing different reagents and are patentably distinct inventions.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter as shown by their different classification.

Further, the search required for Groups I, II, III and IV are not totally coextensive, thus restriction for examination purposes as indicated is proper.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper. Please note that the classifications in the restriction are illustrative only and **do not** represent all the classes and subclasses which must be searched for each invention; nor is the search limited to issued US patents, but rather includes foreign patents and applications as well as literature searches.

5. Newly submitted claims 40-64 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons set forth above.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 40-64 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

6. Currently claims 16-24 are under consideration.

7. Objections and/or rejections of record not reiterated herein have been withdrawn.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 16-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically claims 16-24 are drawn to a method of inhibiting a binding event in a host (*in vivo*) via the administration of an effective amount of a non-naturally occurring bifunctional inhibitor molecule.

Although the specification is enabling for the production and *in vitro* utility of non-naturally occurring bifunctional inhibitor molecules (See assay design and results - pages 20-21), it does not reasonably provide enablement for inhibiting protein-protein interactions *in vivo* with said non-naturally occurring bifunctional molecule.

Firstly, the development of non-naturally occurring/synthetic bifunctional molecules with binding characteristics of interest necessitates several conditions which have not been described in the instant specification. In one instance, the prior art discloses that the development of inhibitors which can bind by both an active site specific interaction to a primary binding site and by a structure nonspecific hydrophobic interaction to a second site (bifunctional or bispecific molecules) requires several parameters to produce the intended binding specificity.

These parameters include; a crystal structure of the enzyme with the bound primary inhibitor, there must be a relatively "open" active site, to permit access to the active site, and the linker must introduce few unfavorable enthalpic and entropic interactions into the bound state. See Jein et al., J Med Chem., 1994, 37, 2100-2105, especially scheme 1 and page 2103, 2nd column 2nd paragraph. These parameters have not been addressed by the instant disclosure. Therefore one of skill in the art would not be able to predict the inhibition by binding of the claimed bifunctional molecule *in vivo*.

Secondly, the specification fails to teach the use of the claimed bifunctional inhibitor molecules in a living organism or host, such that an effective inhibition response is generated. The art has established that the successful production of bifunctional molecules and their utility in assay protocols does not predict their behavior in living animals or a host.

In other words, the bifunctional molecule must be evaluated in a host in order to determine efficacy or inhibition effects. See Kuduk et al. Bio & Med Chemistry Letters, 10, 2000, 1303-1306, in particular page 1305, 2nd column Conclusion, 2nd paragraph.

Further, the art teaches that successful *in vitro* bifunctional construct binding is not always indicative of the *in vivo* results exhibited by that same bifunctional molecule. For example, see Peipp and Valerius page 510 – Conclusion, wherein "Results from clinical trials (in vivo effective dosage) with bispecific antibodies are less encouraging". Peipp and Valerius, Biochemistry Society Transactions, 2002, Volume 30, part 4, pages 507-511.

Accordingly, the specification does not provide substantive evidence that the claimed bifunctional molecules are capable of inhibiting a protein-binding event *in vivo*. This demonstration is required for the skilled artisan to be able to use the claimed bifunctional molecules for their intended purpose of preventing protein binding.

Without this demonstration, the skilled artisan would not be able to predict the outcome of the administration of the claimed bifunctional or bispecific non naturally occurring compositions. The ability to reasonably predict the capacity of a single non -naturally occurring bifunctional molecule to prevent protein-protein interaction in vivo is problematic. Unfortunately, the art is replete with instances where even well characterized compositions that induce an in vitro response fails to elicit *in vivo* utility. See Waldmann, Science, Vol.252, 21 June 1991, pages 1657-1662, in particular page 1657 – 2nd column, wherein antibodies binding therapy has proven elusive and only one monoclonal antibody has been licensed for clinical utility.

Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful binding composition with out prior demonstration of efficacy.

Thirdly, *in vivo* testing or administration to a host entails considerations for host/patient tolerance, differences, validation, and monitoring; which are not set forth in the disclosure. The disclosure merely outlines that the non-naturally occurring bifunctional molecule may be used to treat a variety of diseases, including cellular proliferation, autoimmune disease, cardiovascular diseases, hormonal abnormality, infectious disease, and the like without any supporting data/experimentation. See page 19 lines 24-35.

However, Tockman et al. (Cancer Research 52:2711s-2718s, 1992) teach considerations necessary for a suspected cancer antibody biomarker (intermediate end point marker) to have efficacy and success in a clinical application. See page 2716s. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other compositions being administered and tracked in a host/patient.

Tockman teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials, see abstract.

Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome.

The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. "This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point [marker]", see page 2714s, column 1, Biomarker Validation against Acknowledged Disease End Points section. Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials, see page 2716s, column 2, Summary section.

Tockman reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life expectancies within a population with a disease or disorder are highly speculative and unpredictable.

It has been set forth above that 1) the experimentation required to generate a non-naturally occurring bi-functional molecule which provides binding inhibition such that it would prevent target binding in a living host would be great as 2) there are no immunological experiments provided to demonstrate that the claimed bifunctional compositions are capable of mounting an efficient inhibition response and, more importantly, there are no challenge experiments to demonstrate that a person immunized with any one of the claimed compositions would be treated/protected from a disease.

There are no protocols provided which demonstrate which bifunctional molecules would be effective in immunization, nor are there any protocols detailing the amount of the bifunctional compositions needed to inhibit protein-protein interaction or mount a sufficient immune response in disease treatment, 3) there are no working examples provided in the instant specification, 4) the nature of the invention is a method for producing a non-naturally occurring bifunctional molecule which would provide binding inhibition and treatment in a host, 5) the relevant skill of those in the art is high yet 6) the state of the prior art has been shown to be highly unpredictable as evidenced by prior art afore mentioned, and lastly 7) the claims broadly encompass the administration of compositions to a host (in vivo) to target protein prevent binding in the host, it is therefore set forth that one of skill in the art could not make and/or use the invention without undue experimentation.

Based on the analysis and the teachings presented above it would require undue experimentation for the skilled artisan to practice this invention because there is no support in the specification for the enablement of the broadly claimed invention.

Therefore, in view of the insufficient guidance in the specification, extensive experimentation would be required to enable the claims and to practice the invention as claimed.

Response to Argument

9. Applicant contends that the when evaluated in view of the relevant *Wands* factors, the specification clearly enables one of skill in the art to practice the subject invention without undue experimentation. This argument has been carefully considered but not found persuasive for the following reasons:

(1) The quantity of experimentation necessary

Applicant argues that the quantity of experimentation required to practice the subject invention is reasonable because the art typically engages in such experimentation. Specifically, applicant argues that practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. This argument was carefully considered but not found persuasive because the specification must teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention. In re Gardner, 166 USPQ 138 (CCPA 1970). Applicant has not disclosed any methods of using the bifunctional inhibitor *in vivo* to accomplish the claimed outcome. It is recognized that experimentation is required to optimize methods that have been outlined in protocols for practice, however the instant specification never gives a starting protocol to achieve the desired inhibition. Therefore one of skill in the art would have no clue as to what would be an effective amount of bifunctional molecule to employ, the appropriate route of administration (IP, subcutaneous, IV, oral), or the indicator to measure and determine if the desired effect was achieved (undue experimentation). The prior art teaches that extensive experimentation must be performed to determine efficacy and success in clinical applications (in vivo). For example see, Ivery (Medicinal Research reviews, 2000, 20(6), 452-484) teaching peptidylprolyl isomerase (PPIases) and immunophilins binding reactions (taught in the instant specification on page 9 lines 9-23 as blocking proteins of particular interest). Ivery discloses that this event has been difficult to elucidate and is still controversial *in vivo*. See abstract.

Also, Tockman (Cancer Research 52:2711s-2718s, 1992) discloses that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. See abstract and page 2716s.

Applicant also contends that research articles published after the filing date of the present application, report successful use of the bifunctional inhibitor molecule to inhibit target and binding protein interaction *in vivo*. In support of this position the reference of Gestwicki et al. are present as Exhibit A. This argument was carefully considered but not found persuasive because Gestwicki et al. does not teach in vivo applications of the bifunctional molecule, but merely set forth in vitro analyses (cultured cells). Applicant is invited to show support for *in vivo* or clinical testing in Gestwicki et al.

Accordingly it is maintained that the practice of the instant invention requires undue experimentation.

(2) The amount of direction or guidance presented

Applicant contends that the specification provides ample guidance and direction to practice the claimed invention because the bifunctional inhibitor protein is described, the methods of making the bifunctional inhibitor protein are described, and the in vivo possibilities are set forth (pages 17 through 20). This argument was carefully considered but not found persuasive because the instant invention is directed to *in vivo* administration of the bifunctional inhibitor molecule while the disclosure provides characterization and in vitro response of the bifunctional inhibitor molecule.

However, this does not provide ample guidance with respect to in vivo utility. The prior has shown that *in vitro* response is not sufficient to predict *in vivo* utility. Please see, Peipp and Valerius page 510 – Conclusion, wherein "Results from clinical trials (in vivo effective dosage) with bispecific antibodies are less encouraging". Peipp and Valerius, Biochemistry Society Transactions, 2002, Volume 30, part 4, pages 507-511.

(3) The presence or absence of working examples

Applicant argues that one skilled in the art would be able to extrapolate the disclosure across the entire scope of the claims without excessive and undue experimentation. This argument was carefully considered but not found persuasive because the invention requires undue experimentation for its practice. The prior art has shown that protein-protein interaction *in vivo* is problematic. The ability to reasonably predict the capacity of a single non -naturally occurring bifunctional molecule to prevent protein-protein interaction in vivo is problematic.

Unfortunately, the art is replete with instances where even well characterized compositions that induce an in vitro response fails to elicit *in vivo* utility. See Waldmann, Science, Vol.252, 21 June 1991, pages 1657-1662, in particular page 1657 – 2nd column, wherein antibodies binding therapy has proven elusive and only one monoclonal antibody has been licensed for clinical utility.

Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful binding composition with out prior demonstration of efficacy.

(4) The nature of the invention

Applicant contends that the methods may generally encompass protein biochemistry and small molecule chemistry, which routinely require considerable experimentation. This along with the guidance provided in the specification and Gestwicki et al. demonstrate that the amount of experimentation needed to practice the subject invention is not excessive. This argument was carefully considered but not found persuasive because the specification and Gestwicki et al. do not demonstrate the effects of the bifunctional inhibitor molecule *in vivo*. The art has established that the successful production of bifunctional molecules and their utility in assay protocols does not predict their behavior in living animals or a host. In other words, the bifunctional molecule must be evaluated in a host in order to determine efficacy or inhibition effects. See Kuduk et al. Bio & Med Chemistry Letters, 10, 2000, 1303-1306, in particular page 1305, 2nd column Conclusion, 2nd paragraph.

(5) The state of the prior art

Applicant contends that the invention relates to protein biochemistry and small-molecule chemistry and these fields are well developed. This argument was carefully considered but not found persuasive because the instant invention is not limited to only protein biochemistry and small-molecule chemistry but read on clinical applications (in vivo studies) with the instant bifunctional inhibitor molecule and this is not well developed.

(6) The relative skill of those in the art

Applicant argues that a high level of skill exists in the art and one skilled in the relevant art would be capable of addressing the technical concerns raised by the examiner. This argument was carefully considered but not found persuasive because the "how to use" requirements of 35 USC 112 are not met by disclosing only a pharmacological activity of the claimed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation. *In re Diedrich* (CCPA 1963) supra; *In re Gardner et al.* (CCPA 1970) 427 F2d 786, 166 USPQ 138. In this case the specification merely teaches that the bifunctional inhibitor compound will inhibit binding between (T) and (P) – pharmacological activity, but does not teach how this will be effectively accomplished within a host. Thus the more than technical concerns must be addressed but the entire process and this is undue experimentation.

(7) The predictability or unpredictability in the art

Applicant contends that protein-protein interaction by administration of a bifunctional inhibitor is well developed and taught by Gestwicki et al. and are therefor unpredictable. This argument was carefully considered but not found persuasive because the specification and Gestwicki et al. do not demonstrate the effects of the bifunctional inhibitor molecule *in vivo*. The art has established that the successful production of bifunctional molecules and their utility in assay protocols does not predict their behavior in living animals or a host. In other words, the bifunctional molecule must be evaluated in a host in order to determine efficacy or inhibition effects. See Kuduk et al. Bio & Med Chemistry Letters, 10, 2000, 1303-1306, in particular page 1305, 2nd column Conclusion, 2nd paragraph.

(8) The breath of the claims

Applicant contends that the method can be practiced without undue experimentation because sufficient description and examples are provided in the report of Gestwicki et al. This argument was carefully considered but not found persuasive because Gestwicki et al. does not teach in vivo applications of the bifunctional molecule, but merely set forth in vitro analyses (cultured cells). Applicant is invited to show support for *in vivo* or clinical testing in Gestwicki et al.

Accordingly it is maintained that the practice of the instant invention requires undue experimentation.

10. For reasons aforementioned, no claims are allowed.

Remarks

11. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Weiderrecht et al. (U.S. Patent#5,457,182) teach binding interactions involving FK-506 and FKBP12.6.

B. Maragarnore et al. (U.S.Patent#5,242,810) disclose bifunctional inhibitors of platelet activation and thrombin.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (703) 872-9306, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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